

## REMARKS

Reconsideration of the above-identified application in view of the above amendment and the remarks below is respectfully requested.

Claims 13, 19, 24 and 27-29 have been canceled in this paper. Claims 1, 9, 16, 21, 31, 32, 36 have been amended in this paper. No claims have been added in this paper. Therefore, claims 1-12, 14-18, 20-23, 25-26, 30-36 and 41 are pending and are under active consideration.

Claims 1-36 and 41 stand rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In support of the rejection the Patent Office states the following:

Claims 1, 31, and all claims dependent therefrom recite the limitation "methylation relevant regions" which is considered vague and indefinite. The specification indicates the following with respect to "methylation relevant regions":

"According to the invention it is further preferred to analyse methylation relevant regions comprising the complete genes and/or promoters, introns, first exons and/or enhancers of the genes to be analysed. For the analysis of the methylation sites which are relevant for the expression of a certain gene, but not localized inside the sequence of the gene itself, the effect of the site for the expression of the gene can be readily extrapolated by the person skilled in the art." (page 26, lines 4-11)

However, it is unclear from the specification and the cited portion above what Applicants' regard "relevant" to encompass when applied to "methylation regions". For instance, what criteria(s) or parameters distinguish "methylation regions" to be considered relevant versus irrelevant? Clarification of the metes and bounds, via clearer claim language, is requested.

Claim 1 and all claims dependent therefrom recite the limitation "wherein the gene is selected on the basis of the first knowledge base" which is considered vague and indefinite. The language "selected on the basis" implies some set of features for the gene to be selected, which is unclear. It is therefore unclear what features, per se, of the "first knowledge base" is utilized for gene

selection. Clarification of the metes and bounds, via clearer claim language, is requested.

Regarding claims 9, 21, and 36, the phrase “for example” renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See M.P.E.P. 2173.05(d). Clarification of the metes and bounds, via clearer claim language, is requested.

Regarding claims 16 and 27, the phrase “such as” renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See M.P.E.P. 2173.05(d). Clarification of the metes and bounds, via clearer claim language, is requested.

Claims 13 and 24 recite the limitation “the selection is based on the result of at least two individual rows of analyses” which appears to lack proper antecedent basis. While it is acknowledged that claim 1 indicates the steps of “analysing” and “selecting”, the instant claim fails to provide any indication of “at least two individual rows” in these steps. Clarification of the metes and bounds, via clearer claim language, is requested.

Claim 34 recites the “the identical biological material, different biological material or combination thereof is used in step a)” which lacks proper antecedent basis. Claim 1 step a) recites “isolating at least one biological sample from each of at least two groups of biological material containing mRNA and/or protein”. However, claim 1 (which claim 34 depends from) fails to denote the utilization of “identical biological material, different biological material or combination thereof”. Rather claim 1 utilizes “two groups of biological material containing mRNA and/or protein” and fails to provide any further provisions.

Insofar as the subject rejection pertains to claims 13, 19, 24 and 27-29, the rejection is moot in view of Applicants’ cancellation herein of these claims. Insofar as the subject rejection pertains to claims 1-12, 14-18, 20-23, 25-26, 30-36 and 41, Applicants respectfully traverse the subject rejection.

To the extent that the subject rejection is predicated on the recitation in claims 1 and 31 (and elsewhere) of the expression “methylation relevant regions,” the rejection is now moot since Applicants have deleted this expression from the claims.

To the extent that the subject rejection is predicated on the recitation in claim 1 of the expression “wherein the gene is selected on the basis of the first knowledge base,” the rejection is now moot since Applicants have deleted this expression.

To the extent that the subject rejection is predicated on the recitation in claims 9, 21 and 36 of the expression “for example,” the rejection is now moot since Applicants have deleted this expression from the claims.

To the extent that the subject rejection is predicated on the recitation in claims 16 and 27 of the expression “such as,” the rejection is now moot since Applicants have deleted this expression from the claims.

To the extent that the subject rejection is predicated on the recitation in claims 13 and 24 of the expression “the selection is based on the result of at least two individual rows of analyses,” the rejection is now moot since Applicants have canceled claims 13 and 24.

To the extent that the subject rejection is predicated on the recitation in claim 34 of the expression “the identical biological material, different biological material or combination thereof is used in step a),” Applicants respectfully traverse. At the outset, Applicants note that the word “the” has been removed from the beginning of the expression in question. With this change and in view of the fact that claim 34 depends from claim 32, which requires that steps a) through f) be repeated, Applicants see no inconsistency in having claim 34 recite that the at least two groups of biological material of claim 1 may be identical, different or a combination.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claims 1-8, 19 and 20 stand rejected under 35 U.S.C. 103(a) “as being unpatentable over Huang et al. (Methylation profiling of CpG islands in human breast cancer cells. Human Molecular Genetics. 1999, Volume 8, Number 3, pages 459-470) taken in view of Duggan et al. (Expression profiling using cDNA microarrays. Nature Genetics. January 1999, Volume 21, Number 1, pages 10-14). In support of the rejection, the Patent Office states the following:

Huang et al. describes a novel array-based method (DMH) that allows for a genome-wide screening of hypermethylated CpG island in tumor cells (Abstract). Utilizing different isolated breast cancer cell lines (instant claim 1 step “a”) and instant claims 2-5) the authors detect and select (instant claim 1 steps “b)-c)”) for the mRNA expression level of DNMT1 and p21 (instant claim 6) by Northern Blot analysis (instant claims 7-8) (page 460, left column, lines 26-49; and Figure 1). The authors then proceed to determine the extent of CpG island sequences (i.e. cytosine methylation; instant claims 1 step “d)”) and instant claim 19) undergoing de novo methylation in the six cancer cell lines utilizing MseI enzyme (instant claim 20)(page 460, left column, lines 52-56; and Figure 2). CpG island clones were then selected and gridded on high-density arrays (instant claim 1 steps “e)-f)”) and instant claim 35; pages 460-461, beginning on the right column, line 21). However, Huang et al. does not specifically state the utilization of a database for storing obtained data for the construction of the assay.

Duggan et al. reviews the technical aspects of cDNA microarrays, including the general principles of fabrication of the arrays, target labeling, image analysis and data extraction, management and mining (Abstract). The authors state “All array methods require the construction of databases for the management of information on the genes represented on the array...” (instant claim 1 generating a...”knowledge base”; page 13, right column, lines 30-32).

#### Examiner Comment

Regarding the limitation “knowledge base” the specification provides the following:

“...the knowledge base will comprise only “on” and “off” type of data which allows for a very simple decision between expressed or non-expressed genes.” (page 25, lines 4-6)

Therefore the limitation “knowledge base”, in view of the above, is interpreted to refer to a database of “on” and “off”, per se, gene expression data.

Applicants respectfully traverse the subject rejection.

As best understood, the Patent Office is apparently contending that Huang et al. discloses all of the limitations of the claimed invention, except for “the utilization of a database for storing obtained data for the construction of the array.” Applicants respectfully disagree with the Patent Office’s reading of Huang et al. First, in view of the fact that claim 1 has been amended herein to require that the gene be selected on the basis of the first knowledge base, Applicants respectfully submit that Huang et al. does not teach this limitation. Moreover, Applicants respectfully submit that the Patent Office is in error in asserting that steps (e) and (f) are taught by Huang et al. by virtue of the CpG clones being selected and gridded on high density arrays. Furthermore, Duggan et al. does not provide all of the teachings missing from Huang et al.

Thus, Applicants respectfully submit that step (d) of claim 1 is neither taught nor suggested by Huang et al. While it may be true that the **expression level** of two genes, namely, DNMT1 and p21 was determined by Huang et al., the **level of methylation** of these two genes was not determined. It would appear that the information the authors of Huang et al. obtained from the results of the expression level of said genes served only as a basis for the selection of the biological material to analyze, i.e., that it is quite promising to screen cancer cell lines for hypermethylated CpG islands.

Therefore, the approach of Huang et al. and that of the invention are completely different. The generation of gene panels is based on the information about genes that are differently expressed, inter alia, because of a different methylation level of said genes. The method of Huang et al. simply provides results with respect to the methylation status of CpG islands. Thereafter, the exact methylation level has to be determined (p. 463, right column, first paragraph, of Huang et al.) and the different hypermethylated CpG island loci have to be characterized by nucleotide sequencing. Thus, it seems that the creation of gene panels based on the results of Huang et al. is more complicated, quite expensive and time-consuming.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

The disclosure stands objected to for the following stated reasons:

The specification contains several instances (page 2, lines 18 & 19; page 3, lines 10 & 14, and throughout the remainder of the specification) where the format of the first quotation is located incorrectly. For example, referring to page 2, line 18 the following format appears:

“„Proteomics...”

This appears inconsistent with general utilization of quotations. Appropriate correction is requested.

The specification contains a grammatical error on page 37, line 14; wherein “2-D Gelelectrophoresis” should be replaced with “2-D Gel electrophoresis”. Appropriate correction is requested.

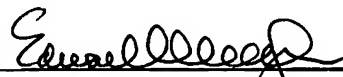
Without acquiescing in the propriety of the objection, Applicants have amended the specification in the manner requested by the Patent Office. Accordingly, the subject objection has been overcome and should be withdrawn.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

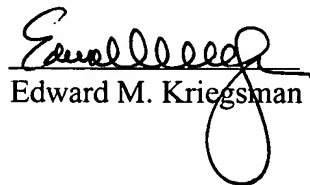
Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on September 26, 2005.

  
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